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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/256,237	02/24/1999	HANS HEINRICH HEIDTMANN	026083/0195	9582

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EXAMINER
DAVIS, MINH TAM B

ART UNIT	PAPER NUMBER
1642	24

DATE MAILED: 05/07/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/256,237	Applicant(s) HEIDTMANN ET AL.	
	Examiner MINH-TAM DAVIS	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-27* is/are pending in the application.

4a) Of the above claim(s) *19-29, 22, 24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21,23 and 25-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Effective February 7, 1998, the Group Art Unit location has been changed, and the examiner of the application has been changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Minh-Tam Davis, Group Art Unit 1642.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant adds new claims 26-27 which are related to claims 21, 23 and 25 and are not new matter.

Accordingly, claims 21, 23, 25-27 are being examined.

The following are the remaining rejections.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

Rejection under 35 USC 112; first paragraph of claims 21, 23, 25 pertaining to lack of enablement for the claimed constructs to function as claimed remains for reasons already of record in paper No.18. New claims 26-27 are rejected for the same reasons already of record in paper No.18.

Applicant argues that the fact that Denmeade speculates as to whether a peptide could be used as a carrier to target products for activation within sites of metastatic prostate cancer producing enzymatic active PSA actually supports the asserted utility,

because this speculation at minimum suggests that the authors believe the asserted utility may be true.

Applicant further asserts that unpredictability of *in vivo* stability of the claimed substrate peptide Arg-Lys-Tyr for PSA is not an appropriate basis for rejection of the claims. The burden of the Examiner is to show a preponderance of evidence, not speculation, that the utility is not credible. There has been no evidence cited to show that the claimed substrate peptide is unstable *in vivo*.

Concerning potential problems such as biological stability, half-life, clearance from blood, degradation, immunological activation, inability to penetrate tissues or cells, absorption and insufficient circulation in the target area to carry the formulation in appropriate concentration, Applicant has asserted a specific utility for the invention.

Applicant recites MPEP 2107.01 (III) and the case law *Cross v. Iizuka*, stating that there is correlation between *in vitro* data and *in vivo* use. Applicant asserts that at the time of the invention, tumors require blood in order to grow, and that an invention that interferes with such blood flow could be useful for the treatment of such tumors.

Applicant submits a Declaration by Dr. Kontermann. In the Declaration, Dr. Kontermann recites several references on pages 2-4, again asserts that tumors require blood in order to grow, and that it is possible to interfere with such blood flow by coagulation using coagulation factor X variants with modified activation cleavage sites so they can be activated by tumor-associated proteases, such as PSA. Dr. Kontermann particularly recites Denmeade et al, for the use of PSA *in vitro*, and a recent finding by

DeFeo-Jones et al, for *in vivo* demonstration of the ability of PSA to activate a peptide-doxorubicin prodrug.

The recitation of MPEP 2107.01 (III), and the case law *Cross v. Iizuka*, the submission of a Declaration by Dr. Kontermann and the references recited in the Declaration are acknowledged.

Applicant's arguments set forth in paper No.21 have been considered but are not deemed to be persuasive for the following reasons:

The Declaration by Dr. Kontermann is drawn to a single species that has not yet been shown to be applied broadly to any other untested contructs to function *in vivo* as contemplated. Although a construct comprising an amino acid sequence cleavable by PSA is stable *in vivo*, and could be used for targeting to prostate tissues having active PSA, as taught by DeFeo-Jones et al, it is not necessarily that any amino acid sequence cleavable by a protease of a construct as broadly claimed in claim 25, and the claimed construct having the claimed substrate peptide Arg-Lys-Tyr as claimed in claims 26-27, is specific for the corresponding protease, e.g. PSA, and is stable *in vivo* unless tested as shown by Denmeade et al (of record) for various substrate peptides of PSA (p.4926). Since it is unpredictable that the claimed constructs would be stable *in vivo*, and since the claimed constructs could be cleaved before reaching the target tissues, the *in vivo* function of the claimed construct is questionable.

Concerning correlation between *in vitro* data and *in vivo* use, the case law Cross v. Iizuka is not applicable for the instant application for the following reasons: MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the

invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling." There is overwhelming evidence in the art that treatment of cancer is unpredictable, as taught by Kimmel et al, Freshney, Dermer, Gura, Jain, Curti, and Hatrwell (of record). However, the specification lacks guidance on necessary dosages and treatment schedules for successful using of the claimed constructs in the treatment of cancer *in vivo*. The specification has not shown how to overcome the problem associated with biological stability, half-life, clearance from blood, degradation, immunological activation, inability to penetrate tissues or cells, absorption and insufficient circulation in the target area to carry the formulation in appropriate concentration. The same lack of correlation with *in vivo* treatment apply as well to the claimed treatment of allergies, autoimmune diseases, infection, inflammation, transplant rejection, thrombosis, blood vessel occlusion and tissue injuries.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

Rejection under 35 USC 112, first paragraph of claims 21, 23, 25 pertaining to lack of enblement for any inhibitor remains for reasons already of record in paper No.18.

Applicant argues that inhibitors with moderate or low affinity for the active compound will inhibit the active compound when held in proximity (which means a constantly high local concentration of inhibitors), by means of a linkage. After cleavage said inhibitors are free to dissociate from the enzyme-inhibitor complex, setting free the active compound, which then can exert its function.

Applicant's arguments set forth in paper No.21 have been considered but are not deemed to be persuasive for the following reasons:

Applicant argues limitation (i.e. inhibitors with moderate or low affinity) not in the claims. Further, there is no references cited by Applicant to show that such inhibitors *in vivo* would dissociate from an active compound, or even if dissociated, if said inhibitors would dissociate in sufficiently practical short time for the active compound to effectively exert its function.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

May 3, 2002